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10/719,695	11/21/2003	Leong Ng	ISA-012.01	1345

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EXAMINER
ROONEY, NORA MAUREEN

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,695	NG, LEONG	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18.2004 and 6/29/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending.

2. Applicant's election without traverse of Group I, Claims 1-17 in the reply filed on 8/14/2006, is acknowledged.

3. Claims 18-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-17 are under examination as they read on a method for detecting tissue hypoxia.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

7. Applicant's Information Disclosure Statements filed on 6/18/2004 and 6/29/2004 are acknowledged.

Claim Objections

8. Claims 2 and 8 are objected to because of the following informalities:
In Claim 2, the conjunction "or" should be used when listing the species; and
In Claim 8, applicant has used improper plural form when reciting "the methods" of Claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 1 and Claims dependent thereupon, it is unclear how ORP 150 is detected in the bodily fluid to determine the level of ORP 150. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized and a correlation step describing how the results of the assay allow for the determination. Claim 1 is missing a contact step that would give an indication of how ORP 150 is detected in the bodily fluid sample.

In Claims 5-6, "the immunoassay" lacks antecedent basis in Claim 1.

In Claim 7, “the antibody” lacks antecedent basis in Claim 1.

In Claims 12-13, "the immunoassay" lacks antecedent basis in Claim 8.

Claims 4-6 and 11-13 provide for using an immunoassay, but, since the claims do not set forth any steps involved in the method, it is unclear what method applicant is intending to encompass. A claim is indefinite where it merely recites a use without any

active, positive steps delimiting how this use is actually practiced.

Claims 8 and 11-17 are directed to detection of a second marker whereby an elevated level of a second marker is indicative of an increased risk of heart disease. Applicant provides no support in the specification that any marker other than N-BNP would be useful for determination of an increased risk of heart disease. Since the claims encompass any second marker, including those that have not yet been discovered, a skilled artisan cannot clearly identify what peptides are or are not encompassed by the claimed invention. The instant claims are indefinite.

11. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 claims dependent thereupon are drawn to the ORP 150 protein. Thus, the claims are drawn to a genus of polypeptides that is defined only by name. Applicant is in possession of amino molecule of SEQ ID NO: 2 encoding ORP 150.

Applicant is not in possession of any amino acid sequence encoding ORP 150 as recited in Claim 1. Applicant has disclosed only ORP 150 amino acid of SEQ ID NO: 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims.

Claim 9 is drawn to the natriuretic peptide proteins. Thus, the claims are drawn to a genus of polypeptides that is defined only by name.

Applicant is not in possession of any sequence encoding natriuretic peptide

proteins as recited in Claim 9. Applicant has not disclosed any sequence for BNP or N-BNP, nor have they specifically defined the claimed natriuretic peptide genus; therefore, the skilled artisan cannot envision all the contemplated peptide sequence possibilities recited in the instant claims.

Claim 10 is drawn to the brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (N-BNP) proteins. Thus, the claims are drawn to a genus of polypeptides that is defined only by name.

Applicant is not in possession of any sequence encoding BNP or N-BNP as recited in Claim 10. Applicant has not recited any sequence for BNP or N-BNP, nor have they identified any structural or functional properties of the peptides that would characterize them as BNP or N-BNP; therefore, the skilled artisan cannot envision all the contemplated peptide sequence possibilities recited in the instant claims.

Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

13. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification, <u>while enabled for</u>:

a method for detecting tissue hypoxia in a mammalian subject comprising contacting a bodily fluid sample of said subject with anti-ORP 150 antibody and determining the level of ORP 150 protein (SEQ ID NO:2) in said bodily fluid sample, including plasma, whereby an elevated level of ORP 150 relative to normal is indicative of an increased risk of heart disease that is the result of heart failure, chronic heart failure, coronary artery disease, ischaemic cardiomyopathy, myocardial infarction atherosclerosis, ischaemic stroke, aortic aneurysm or peripheral vascular disease;

the method using lateral flow immunoassay or flow-through immunoassay with monoclonal antibodies specific for ORP 150;

the method for detecting tissue hypoxia in a mammalian subject further comprising detection the BNP or N-BNP second marker in a bodily fluid sample of a mammal, including plasma, whereby an elevated level of the second marker is indicative of heart disease using lateral-flow immunoassay or flow through immunoassay; and

the method for detecting tissue hypoxia in a mammalian subject wherein ORP 150 and/or the second marker are monitored periodically.

The specification does not reasonably provide enablement for:

detection of any "ORP 150" protein without reference to specific structure or function;

detection of ORP 150 protein using antibody without any recited contact step to determine the level of ORP 150;

detection of any second marker, any natriuretic peptide second marker, BNP second marker or N-BNP second marker using antibody without any recited contact step to determine the level of the second marker;

detection of any second marker without reference to specific structure or function whereby an elevated level of a second marker is indicative of an increased risk of heart disease;

detection of any "natriuretic peptide" second marker without reference to specific structure or function whereby an elevated level of a second marker is indicative of an increased risk of heart disease; and

detection of any BNP or N-BNP protein second marker without reference to specific structure or function whereby an elevated level of a second marker is indicative of an increased risk of heart disease.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The specification does not reasonably provide enablement for detecting any ORP 150 protein as recited in Claim 1.

The specification does not reasonably provide enablement for detecting any "second marker" protein as recited in Claim 8.

The specification does not reasonably provide enablement for detecting any "natriuretic peptide" as recited in Claim 9.

The specification does not reasonably provide enablement for detecting "BNP" or "N-BNP" in bodily fluid as recited in Claim 10.

The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, without sufficient guidance, the changes which can be made in the structure of a protein, that still maintains activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The specification does not reasonably provide enablement for any method of detection of ORP 150 as recited in Claim 1. Also, an antibody contact step is required to enable the claims. There is insufficient guidance in the specification to enable claims including all methods of detection.

The specification does not reasonably provide enablement for any method of detection of a second marker as recited in Claim 8. The method of detection of Claim 8 is not limited to the bodily fluid sample of Claim 1. In Claim 8, the second marker could be detected independently of the method of detection of ORP 150. There is insufficient guidance in the specification to enable claims including all methods of detection. An antibody contact step is required to enable the claims.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

15. Claims 1-4, 7-11 and 14-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,948,637 in view of Hall et al. (PTO 1449 filed 6/18/2004, Reference AG).

The 637' patent claims the purified human ORP-150 protein of SEQ ID NO: 1 (identical to SEQ ID NO: 2 of the instant application over length and sequence), monoclonal antibodies to the ORP 150 protein and a method of diagnosis of ischemic diseases in a patient by detecting the ORP 150 polypeptide that is induced under hypoxic conditions (In particular, abstract, column 1 lines 41-67, column 2 lines 11-14, column 4 lines 46-67 and column 5 lines 1-12).

The prior art differs from the claimed invention by the recitation of detection of ORP-150 in a bodily fluid sample (Claim 1) such as plasma (Claims 3 and 14) by immunoassay (Claim 4) and by detection of a second marker indicative of an increased risk of heart disease (Claim 8) by immunoassay (Claim 11) and monitoring over a series of timepoints (Claims 16-17).

Hall et al. teaches detection of natriuretic peptide, particularly N-terminal pro-brain natriuretic peptide and brain natriuretic peptide, in the diagnosis and management of heart failure patients. The reference teaches that the determinations should be combined with other diagnostic examinations, including other peptide determinations to improve diagnostic performance and that it can be done over a series of time points to better monitor disease (In particular, page 395, fourth paragraph, page 396, fourth paragraph and page 397, last paragraph). The reference also teaches the ease of detecting the proteins in a patient's plasma (In particular, page 395, third paragraph and page 396, first and last paragraphs) and detection by immunoassay (In particular, pages 395, second paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to detect ORP 150 protein in a patient to detect increased risk of heart disease in bodily fluid, such as plasma, using monoclonal antibodies to the ORP-150 protein (637' patent) in an immunoassay (Hall et al.) because immunoassays are specific, reliable and convenient to use. Bodily fluids such as plasma are convenient to obtain from a patient and contain all the requisite proteins necessary for an assay.

It would also be obvious to one of ordinary skill in the art at the time the invention was made to combine the determination of ORP 150 (637' patent) with the determinations of other diagnostic markers, such as natriuretic peptides, for diagnosis of heart failure (Hall et al.), in view of the suggestion in Hall et al. to combine tests to improve diagnostic performance. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

It would also be obvious to one of ordinary skill in the art at the time the invention was made to detect the level of ORP 150 alone or in combination with a second marker

to better adjust a patient's therapy according to their cardiac disease and severity associated peptide levels, as suggested by Hall et al. (In particular, page 396, third paragraph and page 396, second paragraph).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 4-5 and 11-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,948,637 in view of Hall et al. (PTO 1449 filed 6/18/2004, Reference AG) as applied to Claims 1-4, 7-11 and 14-17 above, and further in view of Karl et al. (PTO-1449 filed 6/18/2004, Reference AJ).

The teachings of the 637' patent and Hall et al. have been discussed *supra*.

Claims 5 and 12 differ from the prior art by the recitation of detection of ORP 150 alone or in combination with detection of a second marker using lateral flow immunoassay.

Karl et al. teaches immunoassay reagents and methods for measurement of natriuretic peptides in blood and plasma for diagnosis of cardiac impairment (In particular, abstract, introduction, and page 180, last paragraph). The reference teaches using a sandwich assay to detect NT-proBNP, which is a lateral flow immunoassay as defined in the instant specification.

It would also be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of ORP 150 protein in a patient's bodily fluid, such as

plasma, using monoclonal antibodies to the ORP 150 protein (637' patent) in a lateral flow immunoassay (Karl et al.) to detect increased risk of heart disease. Lateral flow immunoassays, such as sandwich format immunoassays, are efficient " highly sensitive" and "specific" (In particular, page 177, abstract). Bodily fluids such as plasma are convenient to obtain from a patient and contain all the requisite proteins necessary for performing such an assay.

It would also be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of BNP or N-BNP second markers in a patient's bodily fluid, such as plasma, using antibodies to the BNP or N-BNP proteins (Hall et al.) in a lateral flow immunoassay (Karl et al.) to detect increased risk heart disease. Lateral flow immunoassays, such as sandwich format immunoassays, are efficient " highly sensitive" and "specific" (In particular, page 177, abstract). Bodily fluids such as plasma are convenient to obtain from a patient and contain all the requisite proteins necessary for performing such an assay.

It would be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of ORP 150 and BNP or N-BNP with a lateral flow immunoassay because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 4, 6, 11 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,948,637 in view of Hall et al. (PTO 1449 filed 6/18/2004, Reference AG) as applied to Claims 1-4, 7-11 and 14-17 above, and further in view of May et al. (PTO-892, Reference A).

The teachings of the 637' patent and Hall et al. have been discussed *supra*.

Claims 6 and 13 differ from the prior art by the recitation of detection of ORP 150 alone or in combination with detection of a second marker using flow-through immunoassay.

May et al. teaches a specific, flow-through immunoassay for determining pregnancy that reacts a liquid biological sample with a test strip made of dry porous material that absorbs the liquid biological sample and transports the biological sample to a membrane zone with immobilized antibody to hCG. If the antigen is present in a biological sample, a colored spot develops on the surface of the membrane through use of a color tagged secondary antibody. (In particular, Claims 1-34 and column 2 lines 3-20).

It would also be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of ORP 150 protein in a patient's bodily fluid, such as plasma, using monoclonal antibodies to the ORP 150 protein (637' patent) in a flow-thorough immunoassay (May et al.) to detect increased risk of heart disease. The May et al. reference teaches that such a device is optimal as it is specific, reliable, quick, convenient, commercially available and suitable for home-use because of the lack of requisite skill and ease of obtaining a bodily fluid sample for use (In particular column 1 lines 10-45 and lines 64-67 and column 2, lines 1-2). Bodily fluids such as plasma are convenient to obtain from a patient and contain all the requisite proteins necessary for performing such an assay.

It would also be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of BNP or N-BNP in a patient's bodily fluid, such as plasma, using monoclonal antibodies to the ORP 150 protein (Hall et al.) in a flow-through immunoassay (May et al.) to detect increased risk of heart disease. The May et al. reference teaches that such a device is optimal as it is specific, reliable, quick, convenient, commercially available and suitable for home-use because of the lack of requisite skill and ease of obtaining a bodily fluid sample for use (In particular column 1 lines 10-45 and lines 64-67 and column 2, lines 1-2). Bodily fluids such as plasma are convenient to obtain from a patient and contain all the requisite proteins necessary for performing such an assay.

It would be obvious to one of ordinary skill in the art at the time the invention was made to combine detection of ORP 150 and BNP or N-BNP with a lateral flow immunoassay because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to

5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 31, 2006

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